Viral Shedding Level Dictates Risk of Herpes Transmission

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As many as 16% of adults in the U.S. have genital herpes, which is caused by infection with herpes simplex virus 2 (HSV-2). In other parts of the world the prevalence is much higher, with rates as high as 80% in parts of sub-Saharan Africa. Besides causing painful genital lesions, HSV-2 infection substantially increases the risk of transmitting or acquiring HIV. In populations with high HSV-2 prevalence, 40–60% of new HIV infections may be attributable to HSV-2. Transmission of HSV-2 is known to occur during periodic flare-ups of genital lesions accompanied by viral shedding. However, asymptomatic episodes of high viral shedding also occur and likely account for a majority of transmission events. Joshua Schiffer, Bryan Mayer, Youyi Fong, David Swan and Anna Wald (Vaccine and Infectious Disease Division) set out to pinpoint the threshold amount of HSV-2 copies during viral shedding episodes below which HSV-2 transmission is unlikely to occur. To do this, they generated a mathematical model that simulates the viral dynamics in HSV-2-positive individuals and provides data on the risk of transmission. The study was recently published in the *Journal of the Royal Society Interface*.

Performing analysis on HSV-2 transmission is difficult due to the fact that episodes of viral shedding vary widely in intensity and duration. Furthermore, measuring viral load at time of transmission is not feasible, since viral loads can change substantially over several hours. Therefore, Schiffer and colleagues utilized known characteristics of the biology of HSV-2 to generate a mathematical model in order to simulate viral shedding patterns and estimate risk of transmission.

In order to create the model simulations, a previous retrospective study of discordant couples was utilized to provide data on the median number of sex acts prior to transmission of HSV-2. On average, 40 sex acts were required before transmission occurred. This allowed for the calculation of a viral infectivity parameter, which directly correlated to the rate of transmission. When entered into the model simulations, viral infectivity predicted both the probability of transmission and the viral load in the genital tract when transmission events happened. The outcome from the model simulations was that an intervention that maintains viral load below 10,000 copies would prevent most if not all transmission events.

Antiviral medications can reduce viral shedding episodes both in duration and intensity. However, HSV-2 transmission from patients on therapy still occurs. Schiffer and colleagues had previously shown that this likely stems from the short half-lives of currently available antiviral drugs, resulting in periods of sub-therapeutic drug levels, during which the virus is able to actively replicate and achieve high viral loads in the genital tract (Schiffer *et al.*, 2013). It is during these periods that transmission likely occurs.

The results from the current study point to the possibility of preventing transmission via the use of pharmaceutical interventions able to maintain the viral load below this estimated threshold for transmission. "Approximately 10,000 copies of the virus appears to be a good target. If you can get shedding below that level at all times you are likely to severely limit or eliminate transmission," said Schiffer.

Current drug regimens are unable to achieve this level, but there are other antiviral medications currently coming through the pipeline. A recent study by Dr. Anna Wald and other researchers from the Fred Hutchinson Cancer Research Center showed promising results for a new anti-HSV-2 drug, pritelivir (Wald *et al*., 2014). A decrease in viral shedding was observed even when pritelivir was administered only once weekly, indicating a longer half-life of the drug than current antiviral therapies. Ideally, these clinical trials, together with the mathematical model studies, will ultimately lead to successful treatment and prevention for HSV-2 infection and transmission.

Schiffer JT, Mayer BT, Fong Y, Swan DA, Wald A. 2014. Herpes simplex virus-2 transmission probability estimates based on quantity of viral shedding. *J R Soc Interface*. 11: 20140160.

See also: Schiffer JT, Swan D, Corey L, Wald A. 2013. Rapid viral expansion and short drug half-life explain the incomplete effectiveness of current Herpes Simplex Virus-2 directed antiviral agents. *Antimicrob Agents Chemother* 57(12):5820-29.
Previously covered in November 2013 Science Spotlight.

Wald A, Corey L, Timmler B, Magaret A, Warren T, Tyring S, Johnston C, Kriesel J, Fife K, Galitz L, Stoelben S, Huang M-L, Selke S, Stobernack H-P, Ruebsamen-Schaeff H, Birkmann A. 2014. Helicase-primase inhibitor pritelivir for HSV-2 infection. *N Engl J Med*. 370: 201-10.

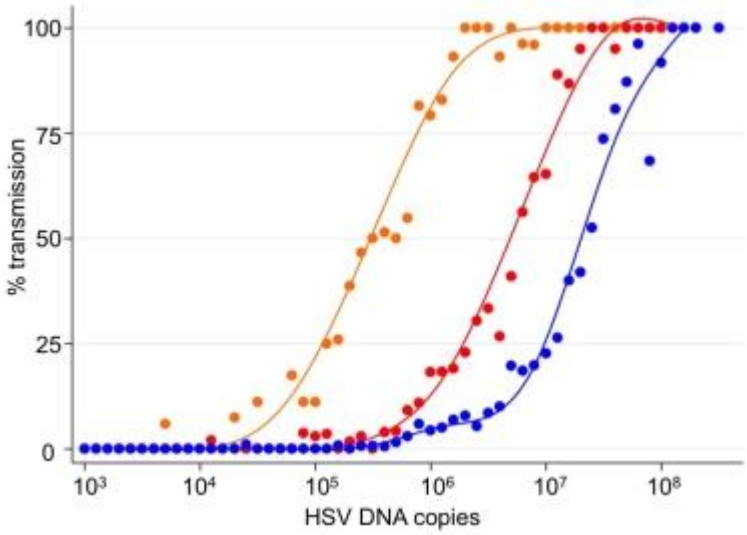

Image provided by Dr. Joshua Schiffer.

The proportion of sex acts resulting in transmission according to HSV viral load as generated by model simulations with three different degrees of viral infectivity: high (orange), medium (red) and low infectivity (blue).